

PATHWAY ANALYSES OF IONIZING RADIATION-RESPONSIVE PROTEINS IN MAMMALS.

Francesco Marchetti¹, Matthew A. Coleman², Andrew J. Wyrobek¹

¹Life Sciences Division, Lawrence Berkeley National Laboratory; ²Biosciences Directorate, Lawrence Livermore National Laboratory.

Exposure of mammalian cells to ionizing radiation can induce changes in protein expression, but little is known of how species and tissues compare in their responses, especially in the low dose range of exposures. We identified mammalian proteins that have been found to respond to ionizing radiation (IR) through a review of over 300 studies published from 1973 through 2006 that used mammalian systems, after either *in vivo* or *in vitro* radiation exposure. This review yielded information on more than 260 genes, including over 170 human proteins, for which proteins showed IR-induced changes in either the levels of expression or posttranslational modifications (e.g., phosphorylation). Most of the studies used high doses of ionizing radiation (>4 Gy) and had no information on dose- or time-responses and only 50 proteins had data from more than one species. The majority of the proteins showed increased amounts or changes in phosphorylation states within 24 hr after exposure (range: 1.5 to 10 fold). Only 32 proteins decreased in amounts in irradiated samples. For eleven proteins there was evidence for both changes in protein levels and posttranslational modifications, while 43 proteins have reported changes in posttranslational modifications without corresponding changes in overall protein levels. Proteins were assigned to three groups based on the dose-range with available information: (1) those with data at doses of 1 Gy and below (low dose group: 47 proteins), (2) those with information at doses between 1 and 4 Gy (medium dose group: 95 proteins) and (3) those with information at doses above 4 Gy only (high dose group: 153 proteins). Proteins associated with cell cycle checkpoint and response to DNA damage were highly represented in all three groups, while proteins associated with apoptosis were found most prominently in the medium and high dose group. Further, network analyses conducted using the Ingenuity software showed similarities among the networks of the three dose groups with Tp53, JUN, and TNF representing major network nodes for all three groups. However, the number of proteins with reported changes within each network, including the major nodes, increased with increasing doses.

Six of the 47 proteins that were responsive at doses of 1 Gy and below showed phosphorylation changes at doses below 10 cGy. These included mitogen-activated protein kinases involved in signal transduction such as ELK1, MAPK3, MAP2K1, and MAP2K1. The major network associated with doses below 10 cGy does not contain proteins involved in DNA repair or cell cycle control but is composed exclusively of proteins involved in signaling pathways such as ERK/MAPK and several interleukin-associated signaling.

Our review of the literature highlighted the paucity of proteomic data currently available in the low dose range. This is contrast to the large number of genes that have already been identified as low-dose responsive by transcriptional studies. Although limited to a few proteins, this data suggests that the proteomic response at low dose is different from that at higher doses and that the low dose proteomic network functions are related to signal transduction.

[Supported by the U.S. Department of Energy under Contract Nos. W-7405-Eng-48 and DE-AC02-05CH11231 with funding from the DOE Low Dose Radiation Research Program]